IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Application Number	: 10/580,248	Confirmation No.:	6084
Applicant	: Mimi ADACHI, *et al.*		
35 U.S.C. § 371 Date	: July 20, 2006		
Title	: METHOD FOR PROLIFERATING CARDIOMYOCYTES		
TC/Art Unit	: 1632		
Examiner:	: Magdalene K. Sgagias		
Docket No.	: 64517.000003		
Customer No.	: 21967		

REPLY BRIEF

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In response to the Examiner's Answer dated March 3, 2010 ("Answer"), maintaining the rejection of pending claims 1, 4-12, 15-25, 31, 34, and 35, Appellants respectfully submit the following Reply Brief.

I. Status of the Claims

Claims 1, 3-31, 34 and 35 are pending. Claims 3, 13, 14, and 26-30 stand withdrawn. 1, 4-12, 15-25, 31, 34, and 35 stand rejected. The rejections of claims 1, 4-12, 15-25, 31, 34, and 35 are appealed.

II. Grounds of Rejection to be Reviewed on Appeal

The following grounds of rejection are to be reviewed on appeal:

1) The rejection under 35 U.S.C. § 103(a) of claims 1, 4-12, 15-25, and 31 based on Tamamori-Adachi, *et al.* (2003) Circ. Res. 92:e12-e19 ("Adachi") in view of Sutterlüty, *et al.* (1999) Nature Cell Biology 1: 207-214 ("Sutterlüty"); Sherr and Roberts (1999) Genes & Development 13:1501-1512 ("Sherr"); Flink, *et al.* (1998) J. Mol. Cell. Cardiol. 30: 563-578 ("Flink"); and Poolman, *et al.* (1999) Circ. Res. 85: 117-127 ("Poolman").

2) The rejection under 35 U.S.C. § 103(a) of claims 34 and 35 based on Adachi, Sutterlüty, Sherr, Flink, Poolman, and Carrano, *et al.* (1999) Nature Cell Biology 1: 193-199 ("Carrano").

III. Argument

A. There is no reason to combine the teachings of Sutterlüty, Sherr, Flink, and Poolman with Adachi.

Claim 1, element (c) requires introducing a gene encoding a factor that inhibits the production, function, or action of a Cip/Kip protein into a cardiomyocyte *in vitro*. There is no dispute that Adachi does not teach element (c).[1] As such, the Examiner relies on the combination of Sutterlüty, Sherr, Flink, and Poolman to teach or suggest element (c).[2] As discussed in the Appeal Brief, however, this combination does not teach or suggest element (c).[3] Even if the combination taught claim 1, element (c), which they do not, there is no reason to combine this hypothetical teaching with Adachi.

The Examiner's rationale for combining Sutterlüty, Sherr, Flink, and Poolman is that this combination purportedly suggests that introducing a gene encoding a factor that inhibits the production, function, or action of a Cip/Kip protein into a cardiomyocytes (i.e., claim 1, element (c)) results in proliferation of the cardiomyocytes.[4] As such, the Examiner concludes that one of skill in the art would have been motivated to introduce element (c) into Adachi's system to increase proliferation of cardiomyocytes.[5]

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[1] *See* Answer, page 4 ("Tamamori-Adachi differs from the claimed invention by not teaching the introduction of a gene encoding a factor that inhibits the production or function of Cip/Kip family proteins into cardiomyocyte cultures"); *id.* at page 15 ("...Adachi does not teach element (c)...").

[2] *See id.* at pages 6 and 7 ("As such the combination of Sutterlüty, Sherr, Flink, and Poolman provide sufficient motivation for one of ordinary skill in the art to introduce a gene encoding a factor that inhibits the production or function of $p27^{kip1}$ to the cardiomyocyte system of Tamamori-Adachi in order to promote the progression of terminally differentiated cardiomyocytes through the G1 to S phases.")

[3] *See* Appeal Brief, pages 6-10.

[4] *See* Answer, page 6 ("The combination of Sutterlüty, Sherr, Flink and Poolman suggest the requirement of $p27^{kip1}$ degradation in order for the cells to progress from the G1 to S phase of the cell cycle and the role of $p27^{kip1}$ in terminal differentiation of cardiomyocytes while its loss is associated with cardiomyocyte cell proliferation.")

[5] *See supra*, footnote 2.

Appellants respectfully submit that the Examiner's premise is incorrect. Indeed, as discussed in the Appeal Brief, the evidence of record makes clear that the introduction of element (c) into cardiomyocytes does not result in an increase in the proliferation of cardiomyocytes.[6] For example, the specification teaches that the introduction of Skp2—a gene encoding a factor that inhibits the production, function, or action of a Cip/Kip protein—does not increase the number of cardiomyocytes.[7] The specification also teaches that the introduction of siRNA specific to the $p27^{Kip1}$ gene—i.e., inhibits the production, function, or action of a Cip/Kip protein—does not increase the number of cardiomyocytes.[8] Accordingly, because the introduction of element (c) into cardiomyocytes does not result in an increase in the proliferation of cardiomyocytes, one of skill in the art would not have been motivated to introduce element (c) into Adachi's system to increase proliferation of cardiomyocytes, nor would they have had a reasonable expectation of success of increasing proliferation.

The Court of Appeals for the Federal Circuit has recognized that evidence showing that a proposed modification does not work is persuasive in finding non-obviousness. For example, in *Procter & Gamble Co. v. Teva Pharmaceuticals USA Inc.*,[9] the district court considered evidence relating to the synthesis and testing of a prior art compound (2-pyr EHDP), a claimed compound (3-pyr EHDP), and a positional isomer of these compounds (4-pyr EHDP).[10] Test results demonstrated that 4-pyr EHDP was not active despite its close relationship with the other potent compounds.[11]

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[6] *See* Appeal Brief, pages 10-12.

[7] *See id.* at pages 10 and 11; *see also* Specification, Example 4.

[8] *See* Appeal Brief, pages 11 and 12; *see also* Specification, Example 5.

[9] *Procter & Gamble Co. v. Teva Pharmaceuticals USA Inc.*, 90 USPQ2d 1947 (Fed. Cir. 2009).

[10] *See id.*, 90 USPQ2d at 1951.

[11] *See id.*

The Federal Circuit agreed with the district court's conclusion that, in view of this evidence, one of skill in the art would not have been motivated to synthesize and test the claimed compound, nor would one have had a reasonable expectation that the claimed compound would be successful.[12]

Likewise, in the instant case, the evidence of record demonstrates that the introduction of element (c) alone does not result in an increase in the proliferation of cardiomyocytes. Accordingly, Appellants respectfully submit that the actual evidence of record outweighs the Examiner's hypothetical combination. Indeed, the USPTO should not be permitted to trump an actual, real world demonstration with a theoretical construction, as was the case in *Procter & Gamble Co. v. Teva Pharmaceuticals USA Inc.*

B. The evidence of record demonstrates unexpected results.

As discussed above and in the Appeal Brief, the specification demonstrates that the introduction of a molecule that inhibits the production, function, or action of Cip/Kip protein does not result in the proliferation of cardiomyocytes. Indeed, Examples 4 and 5 show that the introduction of Skp2 or p27 siRNA alone into cardiomyocytes did not result in an increase in the cell number of cardiomyocytes. As such, one of ordinary skill in the art would have expected that if Skp2, for example, was introduced into cardiomyocytes and co-expressed with other genes (e.g., cyclin D and CDK4), there would not be an increase in proliferation of the cardiomyocytes as compared to the co-expression of these other genes (e.g., cyclin D and CDK4) alone. The specification teaches, however, that the co-expression of Skp2, cyclin D, and CDK4 resulted in a significant increase in cell number as compared to the co-expression of only cyclin D and CDK4.[13] This result is surprising and unexpected.[14]

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[12] *See id.*

[13] *See* Specification, Example 4.

[14] Appellants have also shown that the introduction of Skp2, cyclin D, and CDK4 into cardiomyocytes improves cardiac function. *See* Specification, Example 6.

The Examiner contends that there is no evidence of unexpected results.[15] Specifically, the Examiner asserts that Appellants "have not provided evidence that following co-expression of Skp2, cyclin D, and CDK4 would not result in increased cell proliferation as compared to expression of these genes alone in cardiomyocytes."[16]

Appellants respectively disagree. Appellants have demonstrated that (i) the closest prior art (i.e., Adachi), which teaches the introduction of elements (a) and (b) into cardiomyocytes, increases the number of cardiomyocytes to a certain level; and (ii) the introduction of element (c) into cardiomyocytes does not increase the number of cardiomyocytes. Therefore, one of skill in the art would expect that the introduction of elements (a), (b), and (c) into cardiomyocytes would result in cell number that is equivalent to the cell number obtained by introducing elements (a) and (b) into cardiomyocytes. Appellants have shown, however, that the introduction of elements (a), (b), and (c) into cardiomyocytes results in a cell number that is higher than the cell number obtained when introducing only elements (a) and (b) into cardiomyocytes. Accordingly, Appellants maintain that this evidence appropriately demonstrates unexpected results.

IV. Conclusion

In view of the foregoing, Appellants respectfully request that the Board of Patent Appeals and Interferences reverse the prior art rejections set forth in the Office Action, and allow all of the pending claims.

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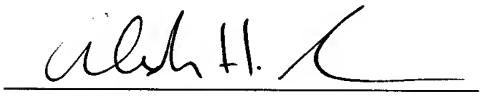
[15] *See* Answer, page 13.

[16] *Id.*

Respectfully submitted,

HUNTON & WILLIAMS LLP

Date: May 3, 2010

By: 

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